Claim	Support in specification
10	p. 11, lines 8-17;
12	Examples 2, 3 and 4;
15	Examples 2 and 4;
16	Examples 2 and 4;
53	Page 23, line 20 - page 24, line 3;
54	Page 16, lines 11-12; page 18, lines 14-22;
55	Page 16, lines 11-12; page 18, lines 14-22;
70	Page 16, lines 11-12; page 18, lines 14-22;
71	Page 16, lines 11-12; page 18, line 23 to page 18, line 28;
72	Page 16, lines 11-12; page 18, line 23 to page 18, line 28;
73	Page 16, lines 11-12; page 18, line 23 to page 18, line 28;
74	Page 16, lines 11-12; page 17, lines 5-19;
75	Page 16, lines 11-12; page 18, lines 8-13; Example 5.C;
76	Page 16, lines 11-12; page 16, line 20 to page 17, line 4; page 17, line 29 - page 18, line 7;
77	Page 16, lines 11-12; page 15, line 21 to page 16, line 2; and
78	Page 16, lines 11-12; page 15, line 21 to page 16, line 2.

As set forth above, these claim amendments are supported by the specification, and no new matter has been introduced.

New claims 70-78 have been added. Claims 10, 12, 15, 16, and 53-55 have been amended to more distinctly point out the subject matter of the Applicants' invention. Following the Examiner's suggestion, claim 10 now recites that the oncogene encodes the proteins that constitute the Markush group. Claim 12 has been amended to recite that the progenitor cell differentiates, rather than "is capable of differentiating," upon inhibition of the expression of the oncogene, or the inhibition of the activity of the protein encoded by said oncogene, as the Examiner has suggested. This Amendment should obviate the Examiner's rejection of claims 13 and 14, as well, as both depend upon claim 12. Furthermore, as claims

50 an 51 were objected to as being dependent upon claim 12, the amendment to claim 12 should satisfy the Examiner's objections. Also following the Examiner's suggestion, claims 15 and 16 have been amended to recite that the cells therein differentiate under appropriate culture conditions. Claim 53 has been amended to specify that the presence or absence of β-III-tubulin is an indicator of the capability of conditionally-immortalized precursor cells can differentiate into neurons, by reciting that β-III-tubulin positive cells differentiate, and cells not positive for β-III-tubulin do not, under cell culture conditions that allow conditionally-immortalized precursor cells to differentiate into neurons. Finally, claims 54 and 55 have been amended to recite that a conditionally-immortalized dorsal root ganglion precursor cell is transplanted into a mammal, conforming the cell that is transplanted to the cell produced in claim 6 or 12, respectively.

Entry of the foregoing amendments and remarks into the file of the above-referenced patent application is respectfully requested. Applicants believe that each ground for rejection has been successfully overcome or obviated. After entry of this amendment, Claims 6-16 and 47-78 will be pending. Claims 6-9, 47 and 48 have been allowed. For the reasons stated above, Applicants believe that the claims are now in condition for allowance.

Rejections Under 35 U.S.C. § 102(e) Over Stringer *et al.*

The Examiner believes that claims 49 and 52 are anticipated by Stringer, U.S. Patent No. 6,197,585 B1 (2001). Stringer purports to disclose, *inter alia*, certain CNS neurons produced from conditionally-immortalized precursor cells. However, Stringer never disclosed the production of *PNS* cells from conditionally-immortalized precursor cells, as have Applicants. PNS and CNS cells are quite different. *See, e.g.*, Goldberg and Barres, "The Relationship Between Neuronal Survival and Regeneration," *Annu. Rev. Neurosci.* 23:579-612 (2000). For example, PNS cells may regenerate, but CNS cells cannot. Furthermore, and relevant to the instant application, CNS cells cannot sense pain; the PNS cells of the invention can and do. CNS and PNS cells substantially differ in both physiology and function; thus, disclosure of the CNS cells of Stringer cannot anticipate the PNS cells of the instant invention. Applicants submit that claims 49 and 52 are therefore in condition for allowance.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 10, 13, 15, 16, 53, 54 and 55 under 35 U.S.C. § 112, second paragraph. Applicants appreciate the Examiner's suggestions as to the claim language therein, and have amended these claims accordingly. Therefore, claims 10, 13, 15, 16, and 53-55 should now be in condition for allowance.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has also rejected claims 54-69 under 35 U.S.C. § 112, first paragraph, for failure to provide an enabling disclosure. Applicants respectfully disagree for the following reasons.

The Examiner believes that there is an insufficiently enabling disclosure for claims 54-59, directed to methods of transplanting conditionally-immortalized dorsal root ganglion progenitor cells into a mammal. Applicants respectfully disagree, and assert that the claims are adequately enabled for the following reasons.

First, the Applicants point out that the reference cited by the Examiner, Jackowski *et al.*, discusses almost entirely the failure of *CNS*, not *PNS* neurons to regenerate. PNS cell regeneration is discussed only in the context of regeneration across the PNS-CNS barrier (*see* page 310, left column). Moreover, the passage cited by the Examiner, page 311, second paragraph, relates to regeneration of injured neurons, not therapies using PNS progenitor cells. The reference is not relevant to the proposition for which the Examiner cited it. In fact, the reference actually states that, in contrast to CNS cells, "a PNS-type environment seems capable of supporting and directing axonal regeneration" (page 308, right column, first paragraph).

Moreover, Claims 54 and 55 do not require therapeutic efficacy; rather, they simply require transplantation of the dorsal root ganglion cell (by known methods) to a mammal. Although the Examiner did not address the utility inherent in such a claim, the specification states that "the PNS progenitor cell lines described herein may be used *in vivo*, in transplantation studies . . . Studies may address the differentiation of the cells when transplanted into the developing or adult PNS." Clearly, claims 54 and 55 contemplate use of the cells of the invention as research tools.

The arguments presented above for claims 54-59 apply as well to new claims 70-73, which differ in that they are directed to the use of differentiated cells as opposed to conditionally-immortalized progenitor cells.

The Examiner also believes that there is an insufficiently enabling disclosure for claims 60-61, directed to methods for screening for an agent that modulates the activity of a protein produced by a dorsal root ganglion cell. The specification is, however, enabling because it refers to techniques that are well-known in the art. A specification is enabling where it, and the relevant art, would allow a person of skill in the art to practice the invention without undue experimentation. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The specification states that a conditionally-immortalized (*i.e.*, undifferentiated) PNS cell line may be used to screen for agents that modulate the activity of a PNS cell protein. (Page 17, lines 5-7). The specification states that the modulation of a protein by a compound may be assessed by examination of the tested compound's effect on transcription, translation, or the activity of the protein itself. (Page 17, lines 5-19.) Determination of each utilizes art that was well-known at the time the application was filed. For example, modulation of transcription was widely known to be assessable using RT-PCR, Northern blots, and dot- or slot-blots. In each case, the means of assessing the increase or decrease in messenger RNA (*i.e.*, agarose gel to detect a PCR product, autoradiogram to detect increased or decreased mRNA content in a blot). For translational modulation, it was well-known that one could compare the amount of a specific protein produced (*e.g.*, by antibodies, immunoassays, protein gels or western blots) to the amount of mRNA produced. For modulation of protein activity, specific targets, such as ion channels, neurotransmitter receptors and transporters, were well-known, as were the means for assessing their activities. Indeed, such targets have been the focus of a number of drug screens. *See, e.g.*, Meldrum, *Epilepsia* 38 Suppl. 9:S7-S15 (1997). The techniques known in the art presented no problems of undue experimentation, as each encompasses standard laboratory procedures. Thus, the art itself presented the parameters to measure to determine whether a specific compound modulates the activity of a protein produced by a dorsal root ganglion cell. The above arguments are applicable to claim 74, which is directed to the use of a differentiated cell rather than a conditionally-immortalized progenitor cell.

The Examiner further believes that claims 62 and 63 are not supported by an enabling disclosure because "the specification does not teach what type of response must be detected

or how it is to be detected." Applicants respectfully disagree and assert that the specification is, indeed, enabling. For example, Example 4 discloses the determination that certain ion channels are present in a cell by examining the changes in sodium current when cells are contacted with an inhibitor, TTX. (Page 30, lines 4-16). The presence of certain N-, L- and P-type channels may be assessed by contacting cells with ω-CTX-GVIA, nimodipine, or ω-Aga-IVA, respectively, and assessing changes in calcium currents. (Page 31, lines 4-9; FIG. 23.) The presence of capsaicin receptors can be assessed by contacting cells with capsazepine and noting any change in capsaicin-mediated current. (Page 31, lines 23-27; FIG. 26). The specification also discloses that differential display may be used to assess the response of the cell. (Page 18, lines 8-13.) Thus, changes in gene expression or in the level of a protein may be the response contemplated by these claims. Differential display, of either proteins or of mRNA, was well-known in the art at the time of filing. In the same way, the presence of a protein in a sample can be assessed by contacting the cell with a sample which may contain the protein, and assessing a change in gene expression, protein production, or in specific, measurable currents in the cell. Thus, the specification provides a number of examples of performing the invention of claims 62 and 63; these claims, therefore, are certainly enabled. The above arguments are applicable to claim 75, which is directed to the use of a differentiated cell rather than a conditionally-immortalized progenitor cell.

The Examiner further believes that claims 64 and 65, directed to methods of identifying a human dorsal root ganglion gene or protein, are insufficiently enabled. The Examiner provides no specific argument that these claims are non-enabled. Applicants respectfully disagree, and assert that the claims are enabled for the following reasons. The specification states that the presence of a nucleic acid sequence, such as a gene, may be determined through standard techniques such as PCR or hybridization techniques, such as are discussed in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual* (cited in the specification). (Page 16, lines 22-26). These techniques have been extensively reported and described in the art; thus, there is no need for the specification to replicate them. The only parameters required for "identification" according to the claim is a determination as to whether a PCR product has been produced, or hybridization has taken place.

The specification further states that a particular protein may be detected by an antibody, *e.g.*, in an immunoassay such as those described extensively in Harlowe and Lane, *Antibodies: A Laboratory Manual* (cited in the specification). (Page 16, line26 - page 17, line

4). Again, the only parameter required is a determination that a particular antibody has bound its intended target; methods such determinations were well-known in the art and disclosed, *inter alia*, in the references cited in the specification. Applicants therefore respectfully assert that claims 64 and 65 are sufficiently enabled by the specification, in view of the state of the art. The above arguments are applicable to claim 76, which is directed to the use of a differentiated cell rather than a conditionally-immortalized progenitor cell.

Finally, the Examiner believes claims 66-69, directed to methods of screening for agents that modulate cell death, or proteins that regulate cell death, are insufficiently enabled. Applicants respectfully disagree for the following reasons. Claims 66 and 67 claim methods of identifying agents that affect dorsal root ganglion cell death. One type of cell death referred to in the specification is apoptosis, and is brought about by, *inter alia*, withdrawal of growth factors. (Page 16, lines 21-27.) Evaluation of the effect of a candidate agent on apoptosis is evaluated simply by assessing the percentage of neurons that die (undergo apoptosis) in the presence and absence of the agent. Such techniques were known in the art. For example, Ferrer-Montel *et al.*, "Selected Peptides Targeted to the NMDA Receptor Channel Protect Neurons from Excitotoxic Death," *Nat. Biotech.* 16:286-291 (March, 1998) assessed the ability of small defined peptides to block the apoptotic effect of the NMDA receptor by exposing cells to NMDA (which induces apoptosis) in the absence or presence of the peptides, then determining the percentage of cells that survived. Again, the state of the art at the time of filing was such that techniques required to practice claims 66 and 67 – such as the culture of, and induction of apoptosis in, neurons – need not have been recited explicitly in the specification. These would be techniques readily available to one of skill in the art desiring to practice the invention, and would have required no undue experimentation to achieve. (It is important to note that the claims do not require knowledge of the particular mechanism by which the effect on cell death is achieved, but only how that effect is to be achieved. It is clear that such a determination is straightforward and simple.)

Claims 68 and 69 are directed to methods of screening for a protein that regulates dorsal root ganglion cell death. Again, the state of the art supports enablement of these claims. Techniques for the modulation of the level of expression of a particular protein were well known at the time the application was filed, and include antisense technology (demonstrated to work well in cell culture systems); site-directed mutagenesis; insertion of regulatable promoters into the genome; and transfection of expression vectors from which a

particular protein may be overexpressed. Having such techniques in hand, it would have been straightforward for a person of skill in the art to modify the expression of a protein, and subsequently measure the effect of such an alteration on the death of the cell. As noted above, persons of skill in the art were aware of techniques to induce apoptosis, such as withdrawal of growth factors (as cited by the specification; *see* page 16, lines 1-2) or addition f particular compounds. Thus, the specification, in light of the art at the time of filing, enables claims 68 and 69.

The above arguments are applicable to claims 77 and 78, which are directed to the use of a differentiated cell rather than a conditionally-immortalized progenitor cell.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims as amended should proceed to allowance. No fee, other than for the extension of time, is believed due. However, if a fee is deemed to be required in connection with this paper, please charge Pennie & Edmonds Deposit Account Number 16-1150 for the appropriate amount.

Respectfully submitted,

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Date December 5, 2001

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EXHIBIT A

MARKED VERSION OF THE CLAIMS

U.S PATENT APPLICATION SERIAL NO. 09/060,409

10. (Twice amended) The method of claim 6 wherein the oncogene encodes a protein selected from the group consisting of v-myc, N-myc, c-myc, SV40 large T antigen, polyoma large T antigen, E1a protein of adenovirus, and E7 protein of human papillomavirus.

12. (Twice amended) A conditionally-immortalized dorsal root ganglion progenitor cell containing an oncogene, wherein the cell [is capable of differentiation] differentiates into neurons upon [substantial] inhibition of the [activity] expression of the oncogene, or inhibition of the activity of the protein encoded by said oncogene.

15. (Amended) A cell according to claim 12, wherein the cell [is capable of differentiation] differentiates into sensory neurons under appropriate culture conditions.

16. (Amended) A cell according to claim 12, wherein the cell [is capable of differentiation] differentiates into nociceptive sensory neurons under appropriate culture conditions.

53. (Amended) A method for determining whether conditionally-immortalized dorsal root ganglion progenitor cells are capable of differentiation into neurons, comprising the step of determining the presence or absence of β-III-tubulin positive cells in the proliferative growth condition, [and therefrom determining whether the cells are capable of differentiation into neurons] wherein said β-III-tubulin positive cells differentiate into neurons, and cells that are not β-III-tubulin positive do not differentiate, under cell culture conditions that allow conditionally-immortalized precursor cells to differentiate into neurons.

54. (Amended) A method for transplanting a conditionally-immortalized dorsal root ganglion precursor cell into a mammal, comprising administering to a mammal a cell produced according to the method of claim 6.

55. (Amended) A method for transplanting a conditionally-immortalized dorsal root ganglion precursor cell into a mammal, comprising administering to a mammal a cell according to claim 12.